Title: Delivering the Thinking Healthy Programme for perinatal depression through volunteer peers: a cluster randomised controlled trial in Pakistan

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SUMMARY

Background: The Thinking Healthy Programme (THP), endorsed by WHO, is an evidence-based intervention for perinatal depression. We adapted THP for delivery by volunteer peers (THPP) – lay women from the community – and assessed its effectiveness and cost-effectiveness in Rawalpindi, Pakistan.

Methods: In this cluster randomised controlled trial, 40 village-clusters were equally randomised to intervention (THPP plus Enhanced Usual Care (EUC)) or to EUC-alone. Consenting pregnant women aged ≥18 years who scored ≥10 on the nine-item Patient Health Questionnaire (PHQ-9) were eligible. Follow-up visits were at 3 and 6 months post childbirth. Primary outcomes were depressive symptoms score and remission at 6 months post-childbirth. Secondary outcomes included recovery from depression, levels of disability and perceived social support and child outcomes. All assessors were masked, and analyses were modified intention-to-treat. The trial was registered with ClinicalTrials.gov (NCT02111915).

Findings: Of the 570 women enrolled between 15th October 2014 and 25th February 2016, 227/283 (80%) and 226/287 (79%) women in the THPP plus EUC and EUC-alone groups, respectively, contributed primary outcome data. Compared to women in the EUC-alone group, those in the THPP plus EUC group at 6 months had lower PHQ-9 scores and better proportions of remission, but neither reached statistical significance (standardised mean difference, SMD=-0·13, 95% CI -0·31 to 0·06, p=0·07; 49% vs 45%; Prevalence Ratio PR=1·12, 95% CI 0·95 to 1·29, p=0.14 respectively). Repeated measures analyses over the 6 months post childbirth showed beneficial intervention effects on both PHQ-9 scores (SMD=-0·22, 95%CI -0·35 to -0·09, p=<0·001) and remission (PR=1·15 95% CI 1·02 to 1·28, p=0·02), disability scores (SMD=-0·12, 95% CI -0·25 to 0·01, p=0·03) and perceived social support scores (SMD=0·16, 95%CI 0·03 to 0·29, p=0·01). THPP was associated with slightly higher costs than EUC-alone but significantly better outcome, thereby rendering it a cost-effective intervention; total societal cost per unit improvement on PHQ-9 was US$ 2·65 (95% CI 1·82 to 3·49) at 3 months post childbirth, US$ 1·17 (95% CI -0·53 to 2·88) for the 3-6-month post-childbirth period and US$ 15·50 (95% CI 9·59 to 21·61) over the study period as a whole. There was no evidence of differences in serious adverse events by group.

Interpretation: THPP showed moderate effects on symptom severity and remission from perinatal depression over the 6-month postnatal period among women caring for infants and was also cost-effective. Our intervention delivered by lay peers can be a potential step towards using an untapped human resource to address the treatment gap of perinatal depression.

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INTRODUCTION

Perinatal depression, which occurs during pregnancy or within the first year postpartum, affects around 20-25% of women in low and middle-income countries (LMICs), including Pakistan.[1-3] Perinatal depression is an important public health problem as it is associated with disability and suicide in women, and adverse child outcomes including impaired physical health[1,4] and poor cognitive and socioemotional development.[5] In most low resource settings, perinatal depression is largely undiagnosed and untreated due to human resource constraints and ill-equipped health systems, with up to 90% of those in need untreated.[6]

The Thinking Healthy Programme (THP) for perinatal depression is an evidence-based intervention based on principles of cognitive behavior therapy. It includes strategies incorporating behavioural activation, active listening, collaboration with the family, guided discovery and homework.[7] THP was designed to be delivered by community health workers, and found to be effective in a large community-based randomised controlled trial (RCT) in Pakistan[8], where it more than halved the prevalence of perinatal depression and significantly improved child health outcomes like diarrheal episodes and vaccination coverage.[8] It is the first low-intensity psychological intervention to be adopted by the WHO.[9]

Despite these promising results, efforts at scale-up of THP are limited by competing demands on community health workers' time, as programme priorities remain communicable diseases, nutrition and child survival.[10-12] The treatment gap for perinatal depression remains high for most LMICs and is likely to remain so, given the scarcity of human resource and funds allocated for mental health.

To address this barrier to scale-up, we adapted the THP for delivery by peers, i.e. lay women from the community with no prior health training or experience, but shared socio-demographic and life experiences with the target population.[13] Our formative research indicated that such peers were feasible and acceptable delivery agents for the intervention and could provide us a potential human resource solution to address the treatment gap.[14] The adapted Thinking Healthy Programme-Peer-delivered (THPP) was evaluated for effectiveness and cost-effectiveness compared to enhanced usual care (EUC) in two diverse rural and peri-urban contexts of South Asia (Pakistan and India).[15]

In this paper, we describe the findings of THPP delivered in Pakistan by volunteer peers (called '*Razakaars'*) in a rural underserved population. These peers worked in close collaboration with government Lady Health Workers (LHWs) and delivered the intervention through a mix of individual and group sessions. LHWs are government employed community health workers which have about 25 stipulated duties.[10] She covers approximately 1500 population (200-250 households that are visited monthly). The duties largely entail MNCH preventive, promotive services, eg registering pregnant women, providing family planning services etc. The results of the India trial based in an urban population, where THPP was delivered through individual sessions, are reported in the companion paper.

METHODS

Setting

The trial was conducted in Kallar Syedan, a rural sub-district of Rawalpindi, Pakistan. It is a socioeconomically deprived area with poverty rates over 50%[16], female literacy rates of 45% and high fertility rates (3.8 births per woman).[17] The economy is largely agrarian, with a population consisting of close-knit communities living in villages and large household sizes (average 6·2 persons per household). Health care is provided by village-based LHWs, each responsible for a population of about 1500 with a focus on maternal and child health, and a primary-care facility staffed by a physician, midwife and a paramedic serving a population of about 25,000. About a quarter of all women in rural Rawalpindi suffer from perinatal depression.[8,18]

Study design and participants

The trial was a single-blind stratified cluster RCT. The unit of randomisation was a village-cluster (population of 2400-3600 serviced by 2-3 LHWs). Eligible village-clusters were geographically separate to minimise contamination. 40 village-clusters were randomised equally to intervention (THPP Plus Enhanced Usual Care [EUC]) or control (EUC-alone) groups.

Potentially eligible participants were women in their third trimester of pregnancy aged ≥18 years, registered with the local LHWs and intending to stay in the study area for at least one year. LHWs register all pregnant women in their catchment areas; we approached all the pregnant women on the lists of all the LHWs. About 95% of the women in the study area covered by LHWs. Participants who did not speak Urdu, Punjabi or Potohari, or who needed immediate medical or psychiatric inpatient care were not eligible. Potentially eligible participants were screened for depression with the Urdu version of the Patient Health Questionnaire 9 (PHQ-9)[19] after written informed consent for screening (or witnessed informed consent for illiterate participants; for such women the questionnaires were read out aloud to them and responses marked by trained assessment teams). Women who screened positive (PHQ-9 score ≥10) were consented for baseline interview for enrolment. The PHQ-9 with a cut-off score of ≥10 has shown a positive predictive value of 55[20] and has previously been used in India (Patel, 2017); it has been validated in perinatal depression populations in Pakistan[19] as well as in other LMIC such as in Ghana and shows acceptable criterion-related validity and reliability for screening for depressive symptoms among women in the antenatal and postnatal period.. Ethical approval was obtained from the Institutional Review Boards (IRBs) at the University of Liverpool, the London School of Hygiene and Tropical Medicine (LSHTM), and the Human Development Research Foundation (the trial-implementing institution in Pakistan). The trial protocol has been published previously.[21]

Randomisation and masking

The randomisation list for village-clusters, stratified by 11 union councils, was prepared by an independent statistician using a computerised randomisation sequence. Outcome assessors were blind to allocation at both baseline and follow up assessments, had no interaction with the intervention team and resided outside the study area. Trial Steering Committee (TSC) members, except the data manager (AZ), remained blind to the allocation status until the data were unmasked after interpretation at a TSC meeting on 23 October 2017.

Procedures

After enrolment, a baseline socio-demographic questionnaire was administered to participants to collect data on potential effect-moderators of treatment effects (age, patient expectations at enrolment, baseline chronicity and severity of depression).

As there is non-existent usual care for perinatal depression in Pakistan, participants in the EUC-alone group received standard care from the LHWs. In addition, treatment was enhanced for participants in the EUC group in the following ways: (1) all participants were informed of their screening results; (2) LHWs who had registered these pregnant women were also informed; (3) all the doctors and midwives at the primary health care centres were given the adapted mental health Gap Action Programme (mhGAP) treatment guidelines for perinatal depression[22] which included information on how to refer severe cases and patients with suicide risk to specialist mental health care; and (4) participants were provided with an information sheet including details on where to seek appropriate health care during pregnancy and beyond.

Participants in the intervention group received THPP in addition to EUC. THPP was developed during a two-year formative research phase.[13] The core psychological strategies included behavioural activation; narratives and pictures to gently challenge unhelpful thinking and behaviour, and encourage alternate helpful ones; and simple everyday language that both the peers and the mothers could relate to. Brief class-room training was supplemented with regular group and field-supervision by non-mental health specialists, who in turn were supervised by a specialist therapist (cascade model of training and supervision). THPP consisted of 10 individual and 4 group sessions, each lasting between 30-45 minutes, from the third trimester (antenatal) to the sixth month post-childbirth (postnatal). THPP was front loaded, with 10 of the 14 sessions delivered during pregnancy and in the first 3 months postnatal. This was done to ensure early reduction in maternal depressive symptoms in this critical phase of infant-care.

The peers who delivered THPP were local volunteer married women, around 30-35 years of age who had good communication skills. All had children and possessed a similar educational and socioeconomic background as participants. They were referred to as *Razakaars* which roughly translates to “volunteer helpers” in the local language (Urdu). Additional criteria of peers are published elsewhere.[14] Peers were identified through LHWs and community elders. Recruitment and placement of the peers within the community was done through the primary health care centres and they were introduced in the community through the LHWs. A total of 66 *Razakaars* (3 per village-cluster) were recruited and trained. The peers received no monetary remuneration for the work. *Razakaars* received group supervisions during the trial ensuring fidelity. Their competency was assessed by the trainers using a checklist based on ENACT.[23] The competency was assessed immediately after training and six months post-training. Peers were categorized as competent (and given depressed cases) if they scored at least 70% on the competency checklist. Individual sessions were delivered by the Razakaars at the participant’s homes; while the group sessions at LHW’s health house or a nearby place convenient for participants. Each Razakaar was given a maximum of seven cases (staggered over the trial period) and asked to make the first contact within two to three days of enrolment. Treatment completion was defined as attending at least 10 out of the possible 14 sessions (see in results competency scores and therapy completion findings).

Outcomes

Primary outcomes were depressive symptoms severity (PHQ-9 score) and remission (PHQ9 <5) assessed at 6 months post-childbirth. Remission was originally defined as PHQ-9 score <10 in the published trial protocol[15] however, this was amended to PHQ-9 score <5 as a more robust and clinically meaningful measure of remission[20] after discussion with the TSC prior to finalisation of the analysis plan. We confirmed that we would have adequate power for this outcome in October 2016, using data from the 6 months outcome data pooled across the arms (from the India trial) prior to the end of outcome evaluation. Approval for this change was obtained from the Data Safety Monitoring Board (DSMB) of the National Institute of Mental Health (NIMH) and the IRBs before unblinding.

Secondary outcomes were depressive symptoms score and remission at 3 months post-childbirth, recovery (proportion not depressed at both 3 and 6 months post-childbirth). Secondary outcomes at 3 and 6 months also included disability scores based on the 12-item WHO Disability Assessment Schedule (WHO-DAS 2·0), using the item-response theory based complex scoring method[24], number of days unable to work in the last month, perceived social support (Multidimensional Scale of Perceived Social Support, MSPSS score), exclusive breastfeeding (WHO definition, namely feeding breastmilk exclusively in the previous 24 hours), and infant anthropometry (weight- and height-for-age z scores).

To enable an economic evaluation to be undertaken, the Client Service Receipt Inventory (CSRI)[25] was administered to trial participants, who reported their details, in order to collect information on their use of health services at 3 and 6 months post-childbirth (copy of CSRI can be available on request from the corresponding author). Detailed information was recorded on contacts with a range of providers including average duration and time to access services. Information was collected on any use or tests or investigations as well as medication. Unit costs were calculated for all items of services use data, including medicines, tests, cost of travel to and from the facilities by the participants, salaries and related costs of government care providers, and private consultation fees. Health system costs were derived from in-patient/out-patient costs, costs of laboratory tests/investigations, medications, and intervention delivery (training and supervision of Razaakars) costs (see note under Appendix J for details of the types of costs included in the intervention). Societal costs encompassed health system costs and time/productivity costs (these included travel costs of the participants and accompanying family members associated with accessing OPD or in-patient services as well as any days out of role and any lost wages) covering both trial participants and family members. A human capital approach was adopted, whereby days out of role collected via the CSRI were multiplied by the estimated wage or monetary value of time to give an estimate of lost production (see Appendix J, K and L for details). Costs were estimated in Pakistani Rupees for the year 2015 and converted to US dollars at the end-year rate for that year (105 Rupees to US$ 1) (found at https://www.xe.com/). Cost estimates were computed for a) the 6-month period of service use covering the third trimester and the first 3 months post-childbirth; b) the 3-month period of service use since the 3-month post-childbirth assessment; and c) the total 9-month period of the trial covering the third trimester and the first 6 months post-childbirth.

Unit costs used in the analysis, together with their respective sources, are shown in Appendix M; cost data taken from earlier years was inflated to 2015 levels using the International Monetary Fund consumer price index. We collected information on serious adverse events (SAEs; death of the participant due to any cause, loss of child, suicide attempt, hospitalisation, victimisation, infant abuse/neglect and stigmatisation, reported violence towards others). Apart from these, we collected social-demographic information at baseline.

Statistical analysis

The sample size estimations for the 6-month primary outcomes assumed an intra-cluster correlation of 0·07 in the intervention group and 0·05 in the control group, and loss to follow up of 20%. Our target sample size was 560 participants (third trimester of pregnancy to 6 moths post-childbirth) to provide 90% power to detect a difference for the primary outcome of remission of 65% in the THPP plus EUC group compared to 45% in the EUC-alone group; and 90% power to detect a standardised mean difference (SMD or effect size) of 0·4 for the primary outcome of PHQ-9 score. The original sample size calculations were based on remission (defined as PHQ-9 <10) in the THP trial in Pakistan[8] and conditional power was estimated based on blinded preliminary data from 134 participants in the companion India trial (prevalence of 67% across the two groups), and for symptom severity on the THP trial[8] (using the THP Hamilton Depression Rating Scale at 6 months: THP group mean 4·5, standard deviation 6·0; control group mean 8·7, standard deviation 7·4). We assumed a more conservative effect size to allow for the possibility of contamination between arms and a diluted effect due to the delivery of the intervention by *Razakaars*.

Outcomes were analysed on an intention-to-treat basis, among complete cases and modified to adjust for union council and baseline PHQ-9 score *a priori,* factors showing imbalance at baseline (chronicity of depression), and factors associated with missing 6-month outcome data (time between screening and childbirth; assessed on blinded data). For continuous outcomes, we used linear regression models, with results reported as standardised mean differences (SMD) calculated as the adjusted mean difference between the groups divided by the adjusted within-cluster standard deviation.[26] To account for the village-clustering, we used generalised estimating equations with an exchangeable correlation structure using the "xtlogit, pa" command with robust standard errors. For categorical outcomes, we used logistic regression models, with results reported as prevalence ratios (PR), estimated from models with the following reference categories: union council (largest), moderate PHQ-9 (score 10-14), mean time between screening and birth (3·0 months), and chronicity ≥12 weeks, using marginal standardisation with the delta method for the confidence intervals (CI)[27]. Sensitivity analyses for primary outcomes included random effects models, accounting for missing outcome data using multiple imputation (assuming missing at random) and alternative models for PHQ-9 score (Poisson, with robust standard errors, and negative binomial). For the primary outcomes, we assessed effect-moderation of the treatment effect with *a priori*-defined potential moderators (recognising that power is low). We conducted repeated measures analyses combining the data from 3 and 6 months (using village-cluster as the panel variable),[28] using a normal distribution to obtain p-values as the number of clusters was sufficiently high for this approximation. Windows of -1 to +2 months were permitted for the follow-up visits; in sensitivity analyses these were restricted to -0.5 to +1 months.

Cost-effectiveness analyses were performed from the health system and societal perspectives. Cost estimates were computed for a) the 6-month period of service use covering the third trimester and the first 3 months post-childbirth; b) the 3-month period of service use since the 3-month post-childbirth assessment; and c) the total 9-month period of the trial covering the third trimester and the first 6 months post-childbirth.

We used Ordinary Least Squares regression models, with margins to generate predicted mean costs. All analyses adjusted for the same baseline covariates as the effectiveness analyses. Incremental cost-effectiveness ratios (ICERs) were derived for primary study outcomes using a non-parametric Monte-Carlo bootstrapping technique (with 1000 replications), by random resampling of effectiveness outcomes and costs for THPP plus EUC and EUC-alone groups. Statistical analyses were conducted using Excel 2016 and Stata 14 for the cost-effectiveness analyses, and all other analyses

were conducted in Stata 14. The Data Safety and Monitoring Board independent of the NIMH oversaw the study. The trial is registered with ClinicalTrials.gov, registry number NCT02111915.

Data sharing

Data from our trial has been made available at the LSHTM data repository available at http://datacompass.lshtm.ac.uk/ (doi:10.17037/DATA.00000793).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report, except for LP who was a Scientific Collaborator, under the cooperative agreement that funded the research. SS, IA, AZ, FV, HAW and AR had full access to trial data. SS and AR had final responsibility for the decision to submit for publication.

RESULTS

Between 15th October 2014 and 25th February 2016, 1910 pregnant women from the 40 village-clusters were identified and approached (Figure 1). Of these, 154 (8%) were not eligible and 25 (1%) refused, leaving 1731 (91%) women who were screened using the PHQ-9 questionnaire. Of these women, 1159 (67%) were ineligible and 2 (<1%) refused, leaving 570 (33%) enrolled into the trial, 283 in THPP plus EUC and 287 in EUC-alone groups. The proportions ineligible and refused were similar across the two groups.

The mean age of participants was 27 years, all were married, >90% were not working outside the home, most did not have schooling beyond secondary, and the median baseline PHQ-9 score was 14 (Table 1). There were no major imbalances between the groups, except a slightly higher proportion of women with chronicity of depression ≥12 weeks in the THPP plus EUC versus EUC-alone group (therefore this variable was adjusted for in the outcome analyses).

At 6 months, 227 (80%) and 226 (79%) participants in the THPP plus EUC and EUC-alone groups, respectively, contributed primary outcome data (p=0·70). There was no evidence of a difference in baseline characteristics by availability of 6-month outcome data, except slightly longer time between screening and childbirth for those who do not have primary outcome data (therefore this variable was adjusted for in the outcome analyses; Appendix A); nor by having the visit in the protocol-defined window (Appendix B).

There was some evidence of a beneficial intervention effect on symptom severity at 6 months post-childbirth, with lower PHQ-9 scores in the THPP plus EUC group compared to EUC-alone (SMD=-0·13, 95%CI -0·31 to 0·06, p=0·07, intra-cluster correlation coefficient (ICC) <0·001) (Table 2 and appendix C). There was little evidence of a difference between the groups with respect to the prevalence of remission at 6 months post-childbirth (PR=1·12, 95%CI 0·95, to 1·29, p=0·14, ICC <0·001) (Figure 2). Similarly, there was little evidence of effect modification for either symptom severity or remission (appendices D and E). Primary outcome results were robust to sensitivity analyses restricting the analysis window (appendix F), alternative model specifications and imputation of missing outcome data (appendices G and H).

Figure 2 and Table 2 show the intervention effect, on depression, over the 6 months post-childbirth acorss groups; namely remission and recovery. While other secondary outcomes like disability, support and child outcomes are also shown.

Participants in the THPP plus EUC group were more likely than those in the EUC-alone group to have remission at 3 months (PR=1·18, 95%CI 1·06 to 1·29, p=0·002) and recovery (PR=1·36, 95%CI 1·09 to 1·63, p=0.002)).
Similarly, there was strong evidence that PHQ-9 score at 3 months was lower in the THPP plus EUC versus EUC-alone group (SMD=-0·30, 95%CI -0·48 to -0·11, p<0·001). Disability score (WHO-DAS) was also lower in the THPP plus EUC versus EUC-alone group at 3 months (SMD=-0·15 [-0·34 to 0·03], p<0·001), and to a lesser degree at 6 months (SMD=-0·11 [-0·29 to 0·08, p=0·23).
In contrast, there was some evidence of an effect on social support (MSPSS score) at 3 months (SMD=0·10 [-0·08 to 0·29], p=0·12) compared to a larger effect at 6 months (SMD=0·20 [0·02 to 0·39], p=0·007).
There was little evidence of an intervention effect on number of days unable to work in the last month at either 3 or 6 months (p=0·35 and p=0·71, respectively), exclusive breastfeeding (p=0·48 and p=0·69, respectively), infant height for age (p=0·55 and 0·29, respectively) or infant weight for age (p=0·32 and p=0·50, respectively).

In repeated measures analyses, there was little evidence of group by time interactions therefore we pooled the 3 and 6 month data assuming a constant intervention effect over time (Table 3). We found lower PHQ-9 score, higher prevalence of remission, lower disability score (WHO DAS), and higher social support (MSPSS score) in the THPP plus EUC group versus EUC-alone (p<0·001, p=0·02, p=0·03 and p=0·01, respectively). There was no evidence of a difference in number of days unable to work between the groups (p=0·47).

Overall, 90 (16%) woman had at least one SAE, evenly distributed between the arms (p=0·72; appendix I). The most common SAEs were loss of child, hospitalisations (mainly of the child) and victimisation. There was no evidence of any differences between the groups.

The *Razakaars* achieved 84% competency to deliver THPP sessions. The overall mean number of sessions attended by participants in the intervention group was 10·9 (standard deviation, SD 3·9, range 0-14; out of 14). The mean number of sessions attended during the antenatal period was 3·7 (SD 1·7, range 0-5; out of 5) and during the postnatal period was 7·3 (SD 2·7, range 0-9; out of 9). 201/258 (78%) participants completed treatment.

Service use patterns and the costs of health care as well as foregone time and productivity are detailed in (Appendix J, K and L) for the THPP plus EUC and EUC-alone groups for the entire period of the trial (ie 3rd trimester of pregnancy to 6 months post-childbirth). The THPP intervention itself cost US$ 133 per beneficary to deliver. As summarised in Table 4, overall health system costs including the inervention were somewhat (but not statistically significantly) higher in the THPP plus EUC group at 3 and 6 months post-childbirth, but time and productivity losses were marginally lower. The adjusted mean difference in societal cost (health system and time costs combined) at 3 months post-childbirth was US$ 6·56 (95%CI -44·01 to 57·13) and at 6 months post-childbirth was US$ 2·32 (95%CI -18·04 to 22·68). The small additional societal cost associated with THPP is compensated for by a statistically significant improvement in PHQ-9 scores, resulting in incremental cost-effectiveness ratios of US$ 2·65 (95% CI 1·82 to 3·49) at 3 months post-childbirth, US$ 9·11 (95% CI -17·00 to 35·22) for the period 3 to 6 months post-childbirth and US$ 15·50 (95% CI 9·59 to 21·61) for the period of the study as a whole. In summary, therefore, THPP offers an appreciable improvement in health at a low marginal cost. The probability of this finding is illustrated via the cost-effectiveness planes depicted in Figures 3& 4 illustrating 75% and 81% of the likelihood of THPP+EUC to be more effective but also more expensive than the EUC alone strategy under a health system and societal perspective, respectively. Over a willingness-to-pay threshold of US$ 60 per unit improvement on

PHQ-9, THPP+EUC was found to have an 98% probability of being a cost-effective choice compared to EUC alone (Appendix O)

DISCUSSION

To overcome the intractable barrier of human resource scarcity for mental health interventions in LMIC, we adapted the Thinking Healthy Programme for perinatal depression for delivery by volunteer peers in rural Pakistani settings. We took advantage of close-knit communities and the willingness of local women to take on the role of lay-therapists. Our results show that the intervention had a modest effect on reducing depressive symptoms and disability, and increasing the probability of remission of the depressive episode at 3 months post-childbirth; furthermore, the intervention delivery is low-cost and easily available that even this modest effect could have significant public health impact and that replications are essential. The effects waned by 6 months, possibly due to spontaneous remission of the depressive episode in control women; or them being an active control group. However, the moderate effects of the intervention on depression and disability at 3 months, a period when the mother is actively engaged in infant-care, remains an important finding that has several public health implications.

To our knowledge, this is the first study (alongside the companion paper from India) where an evidence-based psychological intervention has been delivered successfully by lay women from the community with no formal health education or experience. Peers have been employed successfully in other areas of health[29] but not for psychological interventions that are perceived to require a higher degree of skill-set and training. However, we were able to achieve this through careful adaptation of the psychological strategies, so that these became more intuitive and comprehensible to the peers. The peers received brief class-room training accompanied by field training and were able to deliver the intervention to satisfactory fidelity. A high proportion of women (78%) completed at least 10 sessions out of the total possible 14, indicating the acceptability of the peers as delivery agents. Our feasibility studies showed that the depressed women and their family members engaged well with the peers and used these strategies to good effect.[13] This has significant implications for initiatives to scale-up mental health in settings where there is a lack of formal workforce for this purpose. The peers worked in close partnership with the primary care system, forming a template for collaboration between the community and health services that can help address the treatment gap in a humane and feasible manner.

The peers in the Pakistan site were volunteers and received no remuneration for their role. From the initial 66 peers, 45 were still retained in their role three years later; most of those who left did so due to changes in life-circumstances. Vacant positions were rapidly filled. Our formative work indicates that 'altruistic' peer role could be a form of social investment, a currency through which people pay each other. In other words, a peer in these rural settings might expect less direct financial return but may expect 'in-kind' returns from the community in case of need. This engagement of peers with the THPP may also be related to the availability of opportunity for women to progress their personal ambition outside of the family home. In rural Rawalpindi, such opportunities are limited, and therefore such a role may be a valuable stepping-stone towards greater respect from the community. A counter-argument to the employment of volunteers is that it is a form of exploitation, and allows governments to shirk the responsibility of providing public health care which comes at a cost.[30] Evidence shows that the type of remuneration is indeed context-specific and has implications for the acceptability and sustainability of the intervention, and its scaling up.[31]

The reduction in symptom severity, remission and disability was greatest within the first 3 months post childbirth – when the child care by mothers is at a critical stage. This may be explained by the intentional front-loading of the intervention, where 10 out of 14 sessions were delivered before 3 months. Reducing the duration of morbidity and disability in a period of heightened vulnerability for both mother and infant is an important outcome. Notably the intervention also had a sustained effect as seen by repeated measures as well as by recovery and response across the six month post-childbirth period. Recent evidence suggests that women with postpartum depression represent a heterogenous group of clinical subtypes[32] who require varied interventions to help improve long-term treatment outcomes. Thus, our intervention can be conceputualized as the front-line, first step, intervention, in a stepped care system or a collaborative care model for maternal depression.

We propose that mothers who show no response after the first three months of THPP should be offered a higher frequency of sessions during the final 3 months of treatment and/or should be stepped-up to a more intensive intervention delivered by a specialist provider.

Further research is needed to explore if early response predicts long-term outcomes which might pave the way for more personalized allocation of treatment options which could start with provision of THPP to all women with perinatal depression, discontinuation of early responders after a few sessions, and more intensive interventions for non-responders after the first 3 months of treatment (with components added to address any other determinants of perinatal depression eg domestic violence). Such a programme would allow the recovery of as many mothers as possible through the stepped allocation of treatments of different intensities and would be tailored to individual need and response.

The cost of delivering the intervention sessions was low, partly because the volunteers were not remunerated. This resulting in a very cost-effective strategy (an additional unit of improvement on the PHQ-9 symptom severity score costs between US$ 2-20 depending on the period of assessment and analytical perspective taken).

A high proportion (45%) of participants in the EUC-alone group had remission at 6 months (albeit less than what we anticipated based on interim data from the companion India trial (Fuhr *et al*, companion paper), but higher than expected for the initial sample size calculations based on the original THP trial.[8]One possible explanation may be due to the phenomenon of regression toward mean. This is supported by a recent meta-analyses which shows that on average one-third of participants who receive no treatment for depression remit within 6 months post-childbirth.[32] Natural remission seems to be greater for mild and moderate cases with depression.[32-34] In addition it may be plausible that some non-specific elements in the control group may have mediated symptom improvement for EUC participants. Findings from our qualitative study indicate that participants have felt positive about outcome assessments as this provided an opportunity for participants to talk about their mood. This has been noted in other studies as well.[35]

There are some limitations of our study. First, we did not employ diagnostic interviews to ascertain depression. Instead, we have used the PHQ-9, a validated screening tool which is simple to administer and has been used successfully in other studies in Pakistan. It has been validated in perinatal depression populations in Pakistan as mentioned above and other LMIC including in Ghana; PHQ-9 shows acceptable criterion-related validity and reliability for screening for depressive symptoms among women in the antenatal and postnatal period. Second, generalizability of this peer-delivered psychological treatment, in the absence of existing community-based workers (eg Lady Health Workers) may be limited; since the peers worked in close collaboration with the LHWs. Similarly, the generalizability of findings to unmarried or non-pregnant

women will be limited. Finally, a true intention-to-treat analysis was not possible due to missing outcome data for about 20% of participants, but the results using complete case analysis adjusted for factors associated with missingness (primary analysis) and multiple imputation analysis (Appendices G and H) were similar.

We found that the internal validity of the study was high; the trial conduct and analyses were robust; and there was a high participation rate, high adherence to the intervention with good fidelity of the intervention delivery, and low attrition. The companion paper from India has similar findings (Fuhr *et al*, companion paper), indicating that the study has good external validity. We found, across sites, that lay women as peers can feasibly be used for task-shifting mental health interventions in diverse settings and can be considered as the first stage of care in a collaborative care model for perinatal depression. In conclusion, the two studies open a promising avenue for further research if scaled-up versions are tried for bridging the treatment gap for common mental disorder in low-resource settings.

CONTRIBUTORS

SS drafted the paper and all authors reviewed and approved it. SS, IA, DCF, VP and AR were responsible for the design of the trial. NA, IA, AN, SZ, AB, SB, TB, RL, QA, MS were responsible for intervention content and data gathering instruments. SS, AZ and AR were responsible for trial conduct. AZ was responsible for database design and management. HAW, FV, AN, HT, SS were responsible for analyses.

DECLARATION OF INTERESTS

Authors declare no competing interests.

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RESEARCH IN CONTEXT

Evidence before this study

Systematic reviews provide robust evidence that perinatal depression can be effectively managed with psychological treatments, and there is increasing global evidence that non-specialist health workers can effectively deliver such interventions in resource constrained settings.
We conducted a systematic review to update earlier evidence on the topic to assess the effect of (non-pharmacological) psychological interventions on common perinatal mental disorders in LMIC. Seven electronic bibliographic databases including MEDLINE, EMBASE, CINAHL, PsycINFO, the British Nursing Index, the Allied and Complementary Medicine database and the Cochrane Central Register were searched from 1 January 2012 – 1 January 2018 combining search terms for depression and controlled evaluations. The search was restricted to English articles and studies conducted in LMIC. 17 trials on perinatal depression were retrieved. The pooled effect size was -0.695, 95% CI= -0.92 to -0.47 for maternal depressive symptoms. The studies employed a range of delivery agents, including CHWs; however, none of the studies employed peers as delivery agents for the intervention. However, the largest reported effects have been achieved by the Thinking Healthy Program (THP), delivered by community healthcare workers to depressed mothers in rural Pakistan. The intervention based on cognitive behaviour therapy more than halved the rate of depression compared with usual care and led to significant improvements in women's functioning and disability. However, efforts to integrate the intervention in the community healthcare workers' daily routine at scale was compromised by their multiple health care responsibilities. Whether delivery of this intervention by lay persons such as peer volunteers is feasible or effective remains unclear.

Added value of this study

We adapted the Thinking Healthy Programme for delivery by peers working in close collaboration with the community healthcare workers. This study showed that the adapted intervention, which focused primarily on behavioural activation, was acceptable to participants and feasible to deliver by lay volunteer women in the community who had no previous health background. The intervention produced better outcomes than enhanced usual care and led to a moderate effect on symptom severity, remission from perinatal depression, disability severity and perceived social support at 3 months post-childbirth, with better recovery and response over 6 months postnatal. The intervention was also cost-effective.

Implications of all the available evidence

Psychological interventions such as THPP may be considered for scaling-up through peer workers as the first stage of care in a collaborative care model for perinatal depression.

Figures and Tables

Figure 1: Trial profile

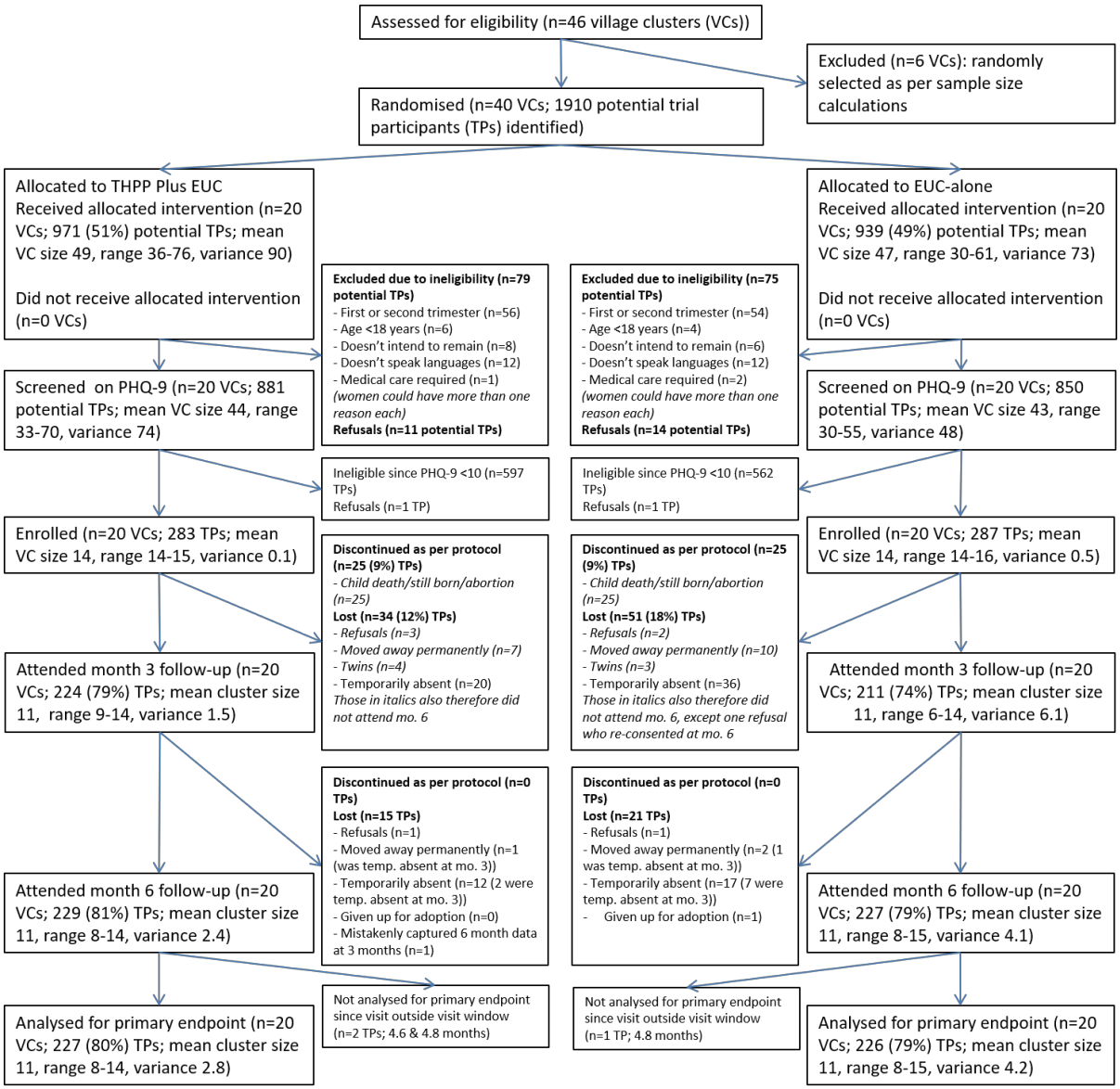


Table 1: Baseline characteristics

	THPP plus EUC (n=283)	**EUC-alone (n=287)**
Age, years (mean [SD])	26.80 [4·60]	27.28 [4·97]
Marital status (n [%])		
Married	283 (100%)	287 (100%)
Occupation (of TP) (n [%])		
Does not work	263 (93%)	270 (94%)
Manual worker	18 (6%)	13 (5%)
Non-manual worker	2 (1%)	4 (1%)
Education status (of TP) (n [%])		
None	52 (18%)	55 (19%)
Primary	68 (24%)	71 (25%)
Secondary	120 (42%)	113 (39%)
Higher secondary	25 (9%)	21 (7%)
Graduate/above	18 (6%)	27 (9%)
Patient's expectation of usefulness of counselling (n [%])		
Not useful	3 (1%)	1 (<1%)
A little useful	12 (4%)	14 (5%)
Somewhat useful	54 (19%)	60 (21%)
Moderately useful	122 (43%)	124 (43%)
Very useful	91 (32%)	87 (30%)
Missing	1 (<1%)	1 (<1%)
Chronicity of depression, weeks (median [IQR])	23 (14-40)	23 (15-34)
Missing *	77 (27%)	94 (33%)
PHQ-9 score [1]		
Median [IQR]	14 [12-17]	14 [12-17]
PHQ-9 score category (n [%])		
10-14 (moderate)	145 (51%)	167 (58%)
15-19 (moderately severe)	99 (35%)	88 (31%)
20-27 (severe)	39 (14%)	32 (11%)
PHQ question 10 (n [%]) [2]		
Not difficult at all	29 (10%)	24 (8%)
Somewhat difficult	76 (27%)	81 (28%)
Very difficult	114 (40%)	118 (41%)
Extremely difficult	64 (23%)	64 (22%)
MSPSS score (mean [SD]) [1]	3.92 [1.41]	3.95 [1.33]
Parity (n [%])		
Primiparous	52 (18%)	50 (17%)
Multiparous	231 (82%)	237 (83%)
Previous miscarriages (n [%])		
None (first pregnancy)	52 (18%)	50 (17%)
None (not first pregnancy)	148 (52%)	144 (50%)
One/more	83 (29%)	93 (32%)
Previous still birth (n [%])		
None (first pregnancy)	52 (18%)	50 (17%)
None (not first pregnancy)	220 (78%)	221 (77%)
One/more	11 (4%)	16 (6%)

	THPP plus EUC (n=283)	EUC-alone (n=287)
Any domestic violence in last 3 months (n [%])		
No	245 (87%)	241 (84%)
Yes	30 (11%)	41 (14%)
Missing	8 (3%)	5 (2%)
Time between screening and birth of child, months (mean [SD])	3·01 [1.27]	2·97 [1.16]
Missing [3]	39 (14%)	46 (16%)

[1] Question: If you checked off any problems (PHQ questions 1-9), how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people? [2] Women who did not attend any follow up visits have missing information relating to the date of birth of the child. PHQ= Patient Health Questionnaire, MSPSS=Multidimensional Scale of Perceived Social Support. THPP= Thinking Healthy Programme Peer-delivered. EUC=enhanced usual care. SD=Standard Deviation. IQR=Interquartile range. * Chronicity was missed being asked in about 1/3rd of our sample

Table 2: Primary and secondary outcomes

	THPP Plus EUC [1] Mean (SD) or n (%)	EUC-alone [1] Mean (SD) or n (%)	Standardised Mean Difference (SMD) or PR (95% CI) for THPP plus EUC vs EUC-alone [2]	ICC [3]	p-value [2]
Primary outcomes					
PHQ-9 score at 6 months	6·02 (5·92)	6·81 (6·22)	SMD= -0·13 (-0·31 to 0·06)	<0·001	0·07
Remission (PHQ-9<5) at 6 months	112 (49%)	101 (45%)	PR= 1·12 (0·95 to 1·29)	<0·001	0·14
Secondary outcomes					
PHQ-9 score at 3 months [4]	6·11 (5.63)	7·82 (6·92)	SMD= -0·30 (-0·48 to -0·11)	<0·001	<0·001
Remission (PHQ-9<5) at 3 months [4]	112 (50%)	93 (44%)	PR= 1·18 (1·06 to 1·29)	<0·001	0·001
Recovery (PHQ-9<5 at both 3 and 6 months) [5]	74 (35%)	51 (26%)	PR= 1·36 (1·09 to 1·63)	<0·001	0·002
WHO-DAS Complex Score					
3 months [6]	15·48 (19.02)	17·50 (18·31)	SMD= -0·15 (-0·34 to 0·03)	<0·001	<0·001
6 months	15·80 (19.83)	18·20 (21.83)	SMD= -0·11 (-0·29 to 0·08)	<0·001	0·23
Number of days unable to work in past 30 days					
3 months [6]	1·28 (4.43)	1·55 (4·70)	SMD= -0·07 (-0·26 to 0·12)	<0·001-	0·35
6 months	1·07 (4·03)	0.97 (3·55)	SMD= 0·02 (-0·17 to 0·20)	<0·001	0·71
MSPSS score					
3 months [4]	4·54 (1·18)	4·41 (1·25)	SMD= 0·10 (-0·08 to 0·29)	<0·001	0.12
6 months	4·74 (1·33)	4·41 (1·37)	SMD= 0·20 (0·02 to 0·39)	<0·001	0·007
Exclusive breastfeeding in last 24 hours					
3 months [4]	99 (44%)	98 (46%)	PR= 0·94 (0·77 to 1·10)	<0·001	0·48
6 months	18 (8%)	19 (8%)	PR= 0·89 (0·38 to 1·40)	<0·001	0·69
Height for age z score					
3 months [7]	0·20 (1·73)	0·05 (1.78)	SMD= 0·05 (-0·14 to 0·24)	<0·001	0·55
6 months [6]	0·26 (1.70)	0·07 (1·92)	SMD= 0·08 (-0·11 to 0·26)	<0·001	0·29
Weight for age z score					
3 months [8]	-1·25 (1·25)	-1·17 (1·22)	SMD= -0·08 (-0·28 to 0·11)	<0·001	0·32
6 months [9]	-0.90 (1·24)	-0·85 (1·18)	SMD= -0·06 (-0·24 to 0·13)	<0·001	0·50

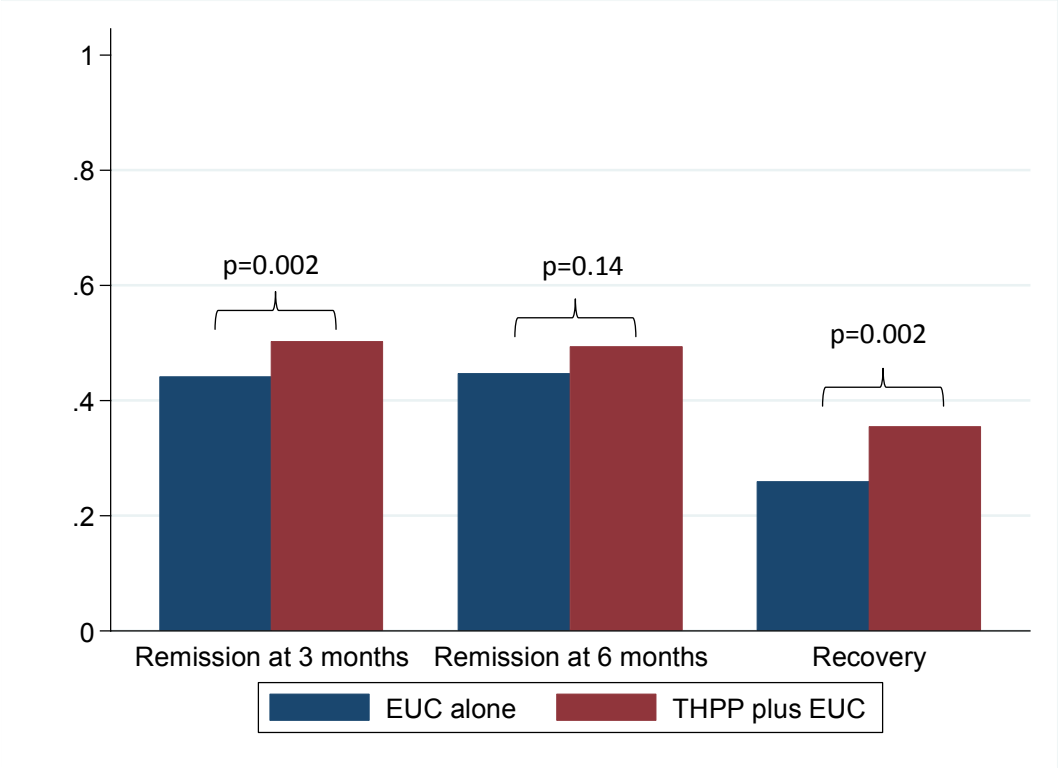
[1] N=227 and 226 in the THPP plus EUC and EUC-alone groups, respectively, unless otherwise indicated. [2] Results from generalised estimating equation models, adjusted for union council, baseline PHQ-9 score, chronicity of depression, and time between screening and childbirth. [3] ICC reported only for primary outcomes. [4] N=223 and 211 in the THPP plus EUC and EUC-alone groups, respectively. [5] N=209 and 197 in the THPP plus EUC and EUC-alone groups, respectively. [6] N=223 and 210 in the THPP plus EUC and EUC-alone groups, respectively. [7] N=217 and 207 in the THPP plus EUC and EUC-alone groups, respectively. [8] N=220 and 209 in the THPP plus EUC and EUC-alone groups, respectively. [9] N=226 and 224 in the THPP plus EUC and EUC-alone groups, respectively. MSPSS=Multidimensional Scale of Perceived Social Support. THPP= Thinking Healthy Programme delivered by peers. EUC=enhanced usual care. PHQ-9=Patient Health Questionnaire 9. WHO-DAS=WHO -Disability Assessment Schedule. PR=Prevalence Ratio. ICC=Intra-cluster correlation. SD=Standard Deviation.

Table 3: Intervention effect for depression, disability and social support outcomes analysed as repeated measures

	P value for group by time interaction	Overall adjusted mean difference or OR (95% CI) for THPP plus EUC versus EUC-alone	Overall adjusted Standardised Mean Difference or PR (95% CI) THPP plus EUC versus EUC-alone	P value for overall effect
Primary outcomes				
PHQ-9 score	0·27	AMD=-1·37 (-2·01 to -0·74)	SMD=-0·22 (-0·35 to -0·09)	<0·001
Remission (PHQ-9<5)	0·86	OR=1·32 (1·06 to 1·65)	PR=1·15 (1·02 to 1·28)	0·02
Secondary outcomes				
WHO DAS complex score	0·89	AMD=-2·47 (-4·70 to -0·25)	SMD=-0·12 (-0·25 to 0·01)	0·03
Number of days unable to work	0·58	AMD=-0·14 (-0·54 to 0·25)	SMD=-0·03 (-0·17 to 0·10)	0·47
MSPSS score	0·24	AMD=0·21 (0·05 to 0·37)	SMD=0·16 (0·03 to 0·29)	0·01

CI=Confidence Interval. PHQ-9=Patient Health Questionnaire (nine items). THPP=Thinking Healthy Program Peer-delivered, EUC=Enhanced Usual Care. MSPSS=Multidimensional Scale of Perceived Social Support. WHO-DAS=WHO Disability Assessment Scale. Results from generalised estimating equation models, adjusted for union council, baseline PHQ-9 score, chronicity of depression, time between screening and childbirth, and visit month.

Figure 2: Intervention effect on remission and recovery by group over 6 months



EUC=Enhanced Usual Care. THPP=Thinking Healthy Programme Peer-Delivered. Remission defined as PHQ-9 score <5; recovery defined as PHQ-9 score <5 at both 3 and 6 months. P-values are from GEE logistic regression models (to account for village clustering), adjusted for baseline PHQ-9 score, union council, time between screening and birth of the child and chronicity of depression (see methods for more details).

Table 4: Cost-effectiveness analysis from health system and societal perspectives at 3 & 6 months post childbirth and over the entire trial period.

	Adjusted mean difference between THPP plus EUC and EUC-alone at 3 months post-childbirth [1] *(Mean, 95% CI)*	Adjusted mean difference between THPP plus EUC and EUC-alone at 6 months post-childbirth [2] *(Mean, 95% CI)*	Adjusted mean difference between THPP plus EUC and EUC-alone over total period of trial [3] *(Mean, 95% CI)*
COSTS			
a. Total Health system costs (incl. intervention)	US$ 9·95 [-35·29 to 55·20]	US$ 4·08 [-1·97 to 10·13]	US$ 19·19 [-22·98 to 61·37]
b. Productivity costs	US$ -3·39 [-20·67 to 13·87]	US$ -1·76 [-18·45 to 14·91]	US$ -1·71 [-4·27 to 6·77]
c. Total societal cost (Health System Cost+ Productivity Costs)	US$ 6·56 [-44·02 to 57·13]	US$ 2.32 [-18·04 to 22·68]	17.48 [-33·28 to 68·25]
OUTCOMES			
1. PHQ-9 summary score[4]	2·21 [1·01 to 3·42]	0·68 [-0·67 to 2·03]	1·51 [0·28 to 2·73]
2. Recovery difference between arms over total period of trial; number of cases (%)[5]	23 (9%)		
	ICER *(US$, 95% CI)*	ICER *(US$, 95% CI)*	ICER *(US$, 95% CI)*
COST-EFFECTIVENESS **A. Total health system costs (incl. intervention)**			
• Cost per unit change on PHQ-9 summary score	4·52 (3·75 to 5·29)	8·62 (2·27 to 14·98)	17·72 (10·92 to 24·51)
• Cost per case recovered (over total trial duration)	236·12		
B. Total costs (health system and productivity costs)			
• Cost per unit change on PHQ-9 summary score	2·65 (1·82 to 3·49)	9·11 (-17 to 35·22)	15·50 (9·39 to 21·61)
• Cost per case recovered (over total trial duration)	215·08		

Notes: ICER, Incremental cost-effectiveness ratio

Reference year 2015; services/costs included in the two totals (health system costs: in-patient/out-patient costs, costs of laboratory tests/investigations, medications, and intervention delivery (training and superivisng Razaakaars); societal costs: health system costs plus time/productivity costs)

[1] Cost and outcome estimates relate to the 6-month period covering the third trimester and the first 3 months post-childbirth

[2] Cost and outcome estimates relate to the 3-month period since the 3-month post-childbirth assessment

[3] Cost and outcome estimates relate to the 9-month period covering the third trimester and the first 6 months post-childbirth

[4] Reduction in PHQ-9 scores converted to a positive change score to aid interpretation of cost-effectiveness results

[5] Recovery is defined as having less than 5 score on PHQ-9 at both 3 & 6 months post-childbirth time points

Figure 3: Cost-effectiveness plane 1: Health system perspective of THPP plus EUC compared to EUC-alone per unit improvement in depression severity score over total period of trial

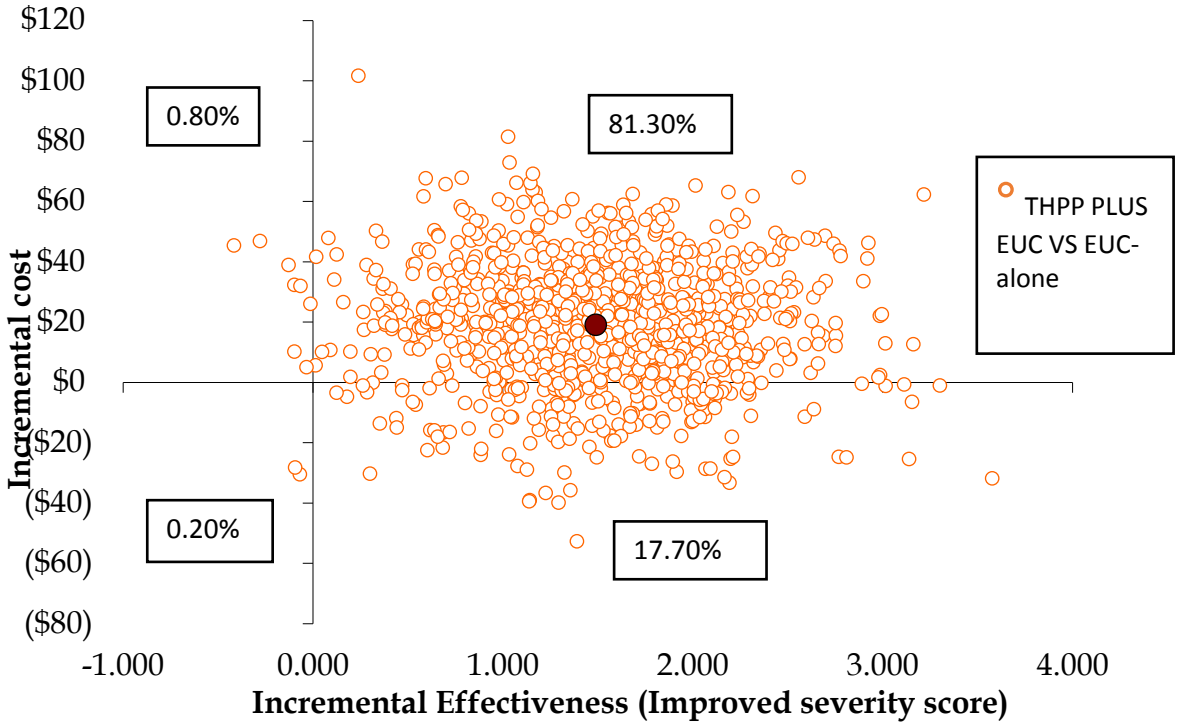
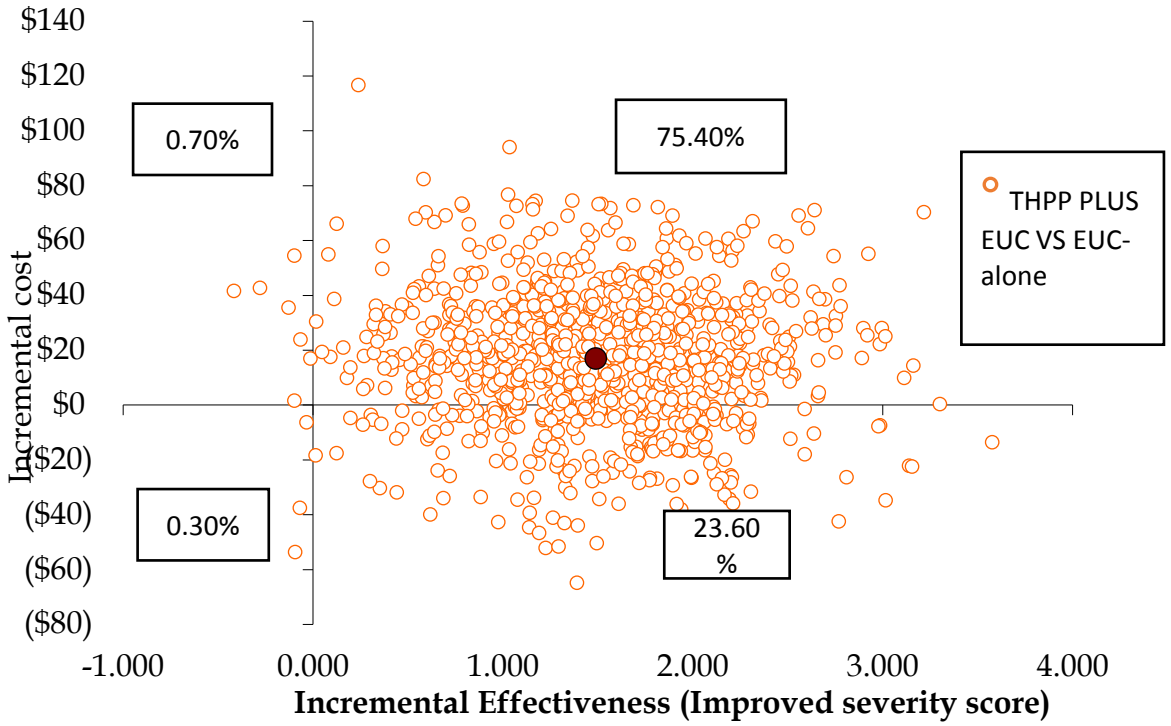


Figure 4: Cost-effectiveness plane 2: Societal perspective of THPP plus EUC compared to EUC-alone per unit improvement in depression severity score over total period of trial



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